Human Psychopharmacology:
Clinical & Experimental

From concept(ion) to life after death/the grave: the 'natural' history and life-cycle(s) of Novel Psychoactive Substances (NPS)

Journal:	*Human Psychopharmacology: Clinical and Experimental*
Manuscript ID	HUP-16-0058.R1
Wiley - Manuscript type:	Special issue on novel psychoactive substances
Date Submitted by the Author:	n/a
Complete List of Authors:	Corkery, John; University of Hertfordshire, Psychopharmacology, Drug Misuse and Novel Psychoactive Substances Research Unit Orsolini, Laura; University of Hertfordshire, Psychopharmacology, Drug Misuse and Novel Psychoactive Substances Research Unit Papanti, Duccio; University of Hertfordshire, Psychopharmacology, Drug Misuse and Novel Psychoactive Substances Research Unit Schifano, Fabrizio; University of Hertfordshire, Psychopharmacology, Drug Misuse and Novel Psychoactive Substances Research Unit
Keyword:	Novel Psychoactive Substances (NPS), life-cycle(s), natural history, monitoring

From concept(ion) to life after death/the grave: the 'natural' history and life-cycle(s) of Novel Psychoactive Substances (NPS)

Abstract:

A range of information needs should be met in order to better understand and predict the longevity/existence of Novel Psychoactive Substances (NPS). This conceptual paper argues that one way of assessing how long a molecule may be around is to document how the life-cycles or natural histories of 'traditional' drugs and NPS evolve. The earliest indication of the possible appearance of a new substance might be evidenced on the DeepWeb. However, this means they are less visible, in line with the clandestine nature of drug use and supply. Therefore, monitoring discussion groups/fora needs the development of new methods compared to those used in the Surface Net. Issues needing consideration in establishing NPS life-cycles are outlined here, together with the probable outcomes that could result. The approach advocated means that it should be easier to identify which NPS are likely to come up or are emerging in real time, and, therefore, pre-empt/prevent their supply.

(153 words)

From concept(ion) to life after death/the grave: the 'natural' history and life-cycle(s) of Novel Psychoactive Substances (NPS)

WHY DO WE NEED TO KNOW NOW ABOUT THE LONGEVITY/EXISTENCE OF NOVEL PSYCHOACTIVE SUBSTANCES (NPS)?

New or novel psychoactive substances are not a recent phenomenon. In the latter decades of the twentieth century new psychoactive substances such as ecstasy (MDMA), 'crack' cocaine and methylamphetamine emerged onto the international recreational drug scene. However, during the first decade of the present century, the 'noughties', there was a marked step-change in this phenomenon – an increasingly accelerated rate of appearance of new or novel substances contrasted with the substances above which are now part of the 'traditional' or established drug scene. Since 2005 this development has been accompanied by increases in the number and variety of molecules and products offered to (potential) consumers (EMCDDA-EUROPOL, 2016; UNODC, 2016). At present, there appears to be little prospect of the situation changing in the short-term.

The accelerating speed and extent of these changes is causing a number of important challenges to various constituencies or stake-holders including: policy-makers, law enforcement agencies, treatment services, epidemiologists, communities and, not least of all, consumers. The key challenges are: how are NPS being created or 'discovered'; what is appearing and when; are they related to existing known molecules; who is producing them and where; how are NPS being advertised and distributed; what is their legal status; what social consequences might arise; what are their likely properties; which and how many adverse health effects, morbidity or mortality can they cause; what the appropriate treatments are; what services might be impacted and how, and over what time-scale(s).

Briefly, these challenges arise from the fact that most NPS are unknown quantities in that they have not been subject to any type(s) of prior testing; therefore, their psychoactive properties (if any), pharmacological, neurophysiological, neuropsychological, psychopharmacological, toxicological, and addiction potential attributes remain unclear. Furthermore, the contents of NPS/'legal high' products offered for sale are unknown to law enforcement agencies, retailers, potential purchasers/consumers, health professionals, etc. and may change over time (Davies *et al*., 2010; Ramsey *et al*., 2010).

The challenges thrown up by this lack of information make it difficult to know if it is necessary to respond to the emergence of a particular molecule and, if a response is considered appropriate, what form(s) that might take. Part of any strategy that needs to be in place for such considerations ought to include an assessment of how long that molecule may remain in circulation and what may be the possible consequences.

One way of assessing how long a molecule may be around would be to compare its known characteristics with that of similar molecules and what happened to them. This means charting the existence of a number of psychoactive substances, including new or novel ones, in order to establish base-lines against which predictive models could be developed and tested. In other words, a series of life-cycles or natural histories of how 'traditional' recreational drugs and NPS evolve need to be documented.

CONCEPTUAL APPROACH

A common approach in describing the stages in the production and consumption of goods is to look at their journey using such metaphors as "from field to fork" or "life is a journey" from "birth to death" or "cradle to grave". In the psychoactive substances field, we developed a conceptual framework for classifying mortality associated with each stage of the khat plant's journey from its cultivation, transportation, consumption, to its effects on the human body. Specifically, we utilised evidence abstracted from observed phenomena derived from a range of sources along that journey to provide a vehicle to identify factors that may impact on the phenomenon of khat-related mortality (Corkery *et al*., 2011).

It is now proposed that a similar approach could be applied to the phenomenon of psychoactive substances, both 'traditional' and 'novel'/'new'. The aim would be to identify initially what the overall timeline and scale is for psychoactive substances, especially 'legal highs'/novel psychoactive substances (NPS), from original concept or creation through to death (of human individuals), or even beyond, i.e. their survival, demise or change following regulation/control.

So far as can be ascertained from internet searches using Google and Google Scholar, this is the first time this approach has been mooted in the published literature in the field of substance (ab)use. However, the notion of "cradle to grave" tracking or monitoring over the life cycle of investigational/experimental products is used in the field of pharmaceutics for accountability, reconciliation, destruction, etc. throughout a product's life cycle (Ma *et al*., 2007; Edwards, 2008). The word 'generation' has been used in recent years to describe new psychoactive products and molecules created and released to replace those existing ones coming under control as a result of legislative actions.

The term 'drug epidemic cycle' (Rose *et al*., 2015) has been used to describe the process by which a 'recreational' drug is first used within a narrowly-defined population or community before becoming main-stream (e.g. the use of methamphetamine in the 'gay' community before moving into the 'club scene') possibly because of its perceived safety, desired effects, and legality before leading to adverse health consequences, then controls, and perhaps leading to reduced consumption. However, this notion does not capture the possibility of re-emergence. Furthermore, 'epidemic' is an inaccurate term in this context.

ASPECTS TO COVER

In the context of the EPS/NPS project (http://www.npsproject.eu/), the authors are involved in studying the role(s) of the Internet, especially the DeepWeb, in the creation, availability, sale, distribution of substances, and dissemination of information about NPS. The idea emerged during a 'brain-storming' session that the earliest indication of the possible appearance of a new substance might be evidenced on the DeepWeb, thereby giving a 'heads-up' or advance warning to relevant stake-holders. This thought was subsequently elaborated into the notion that there may be benefits in looking at the life-cycle or natural history/evolution of specific NPS. Key aspects to try and document include: first appearance on the DeepWeb; migration to the Surface Net/Internet; move into 'head-shops' and/or the 'street' market; notification to formal Early Warning Systems; implementation of legislation to counter the substance; effects of legislation/regulation on availability/use or displacement/substitution; and whether NPS suffer a demise, rebirth/reincarnation/resurrection or alteration/mutation/reinvention. Further details of these aspects and relevant resources are given in Table 1; this is not an exhaustive list.

HOW COULD THIS RESEARCH BE DONE?

Both retrospective and prospective collection of data on NPS and other substances, including those already regulated/controlled would be required in order to get a complete profile of 'traditional' and newly emerging/re-emerging psychoactive substances. Prospective data collection would have to be undertaken on a regular and systematic basis, perhaps with a periodicity as short as a week.

We conjecture that data pointing to the existence of new NPS would first emerge on the DeepWeb - especially DeepNets - before appearing on the Surface Net (Internet) and will be less visible, in line with the clandestine nature of drug use and supply. Therefore, it might be sensible to monitor discussion groups/fora (across several domains/areas of interest – not just users) at specified intervals, say every 2 or 3 weeks, and to take copies/snap-shots of the sites/web-pages to see how things develop over time, and also to see how long it takes before substances are found on the Surface Net.

Methods for online monitoring of the Internet developed by previous projects such as Psychonaut (Deluca *et al*., 2012), ReDNet (Corazza *et al*., (2013), and EU-MADNESS (http://www.eumadness.eu/) would need to be adapted and refined for DeepWeb monitoring as part of the Enhancing Police EPS/NPS project (http://www.npsproject.eu/) and any future work. The key difference would be the use of an Internet communication method intended to enable online anonymity such as TOR (https://www.torproject.org/) when monitoring the DeepWeb, and suitable search engines, e.g. grams (https://www.deepdotweb.com/2014/04/08/grams-darknetmarkets-search-engine/). Search strategies and search terms would need to be developed to monitor the different types of websites, open and hidden, as outlined in Table 1.

Access to other data, including databases, professional networks, and access to informed stake-holders such as members of early warning systems would need to be developed and maintained so that detailed information relating to the data given in Table 1 can be collected on a systematic and routine basis. The types of data to be collected would need to be agreed by participating researchers and data-providers, along with data-sharing and confidentiality protocols, etc. Compilation of data from this multi-disciplinary approach should be centrally co-ordinated, and held in secure conditions with appropriate levels of access.

The aim of the data collection would be to collect data that will lend themselves to the development of mathematical models that will validate existing and new knowledge of 'traditional' recreational substances and facilitate predictions regarding the likely stages and time-scales in the life-cycles of NPS.

LIKELY OUTCOMES OF SUCH RESEARCH

There may be different time-scales for different types of 'traditional' and legal drugs as well as NPS. Old medicines discontinued because of adverse side-effects 'rediscovered' from scanning the patent databases may have a far longer life-story than newer/current medications being abused (e.g. modafinil) or new molecules created to avoid new regulations/controls (e.g. methylphenidate derivatives), but having a shorter history than natural products/plants used for centuries in folk-medicine/religious activities, etc.

This approach should make it faster to track the 'historical evolution of an emerging NPS'. It could be possible to collect more information on a specified drug without waiting for its appearance. The potential insights that could be generated by the proposed approach cover five main domains. First, change over time in: developments in the uses, modes of administration, formulations/preparations, content of products, marketing, supply chains, prices, purities, quantities offered. Second, their first appearance on discussion fora/posts. Third, their first appearance on drug market sites. Fourth, how their markets/availability/attractiveness changes over time, and how these aspects change depending on legal status/notification in a specified country, etc. The legal status of specific molecules may differ in various countries, thereby leading to different patterns in terms of drug availability, use, treatment, etc. Lastly, health risks (acute and chronic physical/mental), morbidity, mortality associated with NPS (production and/or consumption).

However, some considerations will need to be borne in mind. Many NPS appearing as 'products' may be marketed with the same packaging but contain different compounds (Davies *et al*., 2010; Ramsey *et al*., 2010). Therefore, if data are only collected from websites without testing/verifying the chemical composition of these drugs, researchers could collect 'clinical' and 'marketing' data not necessarily associated with an identified chemical composition (Hillebrand *et al*., 2010).

CONCLUSIONS

Taking a holistic approach to NPS allows researchers to identify/think of wider range of dimensions of a phenomenon and what factors may impact on it and how these might be influenced/ tackled in the future if desired/thought practical in order to affect changes. There will be implications for service provision, treatment options, interdiction, monitoring/ surveillance, pharmacovigilance, epidemiology, law-making, education, etc. The approach advocated here should mean that it could be easier to identify which NPS are likely to come up or are emerging in real time, and, therefore, pre-empt/prevent their supply. The lag which academic research currently experiences in respect of the online NPS market (Deluca *et al*., 2012) should be reduced.

FUNDING

This paper was supported in part by grants of the European Commission Project EPS/NPS-Enhancing Police Skills concerning Novel Psychoactive Substances, with the financial support of the European Commission – Targeted call on cross border law enforcement cooperation in the field of drug trafficking - DG Justice/DG Migrations and Home Affairs (JUST/2013/ISEC/DRUGS/AG/6429). http://www.npsproject.eu/

CONFLICTS OF INTEREST

The authors declare that there is no conflict of interest.

REFERENCES

Corazza O, Assi S, Simonato P, Corkery J, Bersani FS, Demetrovics Z, Stair J, Fergus S, Pezzolesi C, Pasinetti M, Deluca P, Drummond C, Davey Z, Blaszko U, Moskalewicz J, Mervo B, Furia LD, Farre M, Flesland L, Pisarska A, Shapiro H, Siemann H, Skutle A, Sferrazza E, Torrens M, Sambola F, van der Kreeft P, Scherbaum N, Schifano F. Promoting innovation and excellence to face the rapid diffusion of novel psychoactive substances in the EU: the outcomes of the ReDNet project. 2013. *Hum Psychopharmacol*. 28(4):317-23. doi: 10.1002/hup.2299. PubMed PMID: 23881879.
http://www.ncbi.nlm.nih.gov/pubmed/23881879

Corkery JM, Schifano F, Oyefeso A, Ghodse AH, Tonia T, Naidoo V, Button J. 2011. Overview of literature and information on "khat-related" mortality: a call for recognition of the issue and further research. *Ann Ist Super Sanita*. 47(4):445-64. doi: doi: 10.4415/ANN_11_04_17. PubMed PMID: 22194080.
http://www.ncbi.nlm.nih.gov/pubmed/22194080

Davies S, Wood DM, Smith G, Button J, Ramsey J, Archer R, Holt DW, Dargan PI. 2010. Purchasing 'legal highs' on the Internet--is there consistency in what you get? *QJM*. 103(7):489-93. doi: 10.1093/qjmed/hcq056. PubMed PMID: 20413562.
http://www.ncbi.nlm.nih.gov/pubmed/20413562

Deluca P, Davey Z, Corazza O, Di Furia L, Farre M, Flesland LH, Mannonen M, Majava A, Peltoniemi T, Pasinetti M, Pezzolesi C, Scherbaum N, Siemann H, Skutle A, Torrens M, van der Kreeft P, Iversen E, Schifano F. 2012. Identifying emerging trends in recreational drug use; outcomes from the Psychonaut Web Mapping Project. *Prog Neuropsychopharmacol Biol Psychiatry*. 39(2):221-6. doi: 10.1016/j.pnpbp.2012.07.011. PubMed PMID: 22841965.
http://www.ncbi.nlm.nih.gov/pubmed/22841965

Edwards AG. 2008. Quality Systems for Drugs and Biologics - FDA is modernizing and streamlining current good manufacturing practices. *Pharmaceutical Technology*. 32(2). Available at: http://www.pharmtech.com/quality-systems-drugs-and-biologics-0?id=&sk=&date=&&pageID=1
Accessed 8 July 2016.

European Monitoring Centre for Drugs and Drug Addiction and Europol. 2016. EU Drug Markets Report: In-Depth Analysis, EMCDDA–Europol Joint publications, Publications Office of the European Union, Available at:
http://www.emcdda.europa.eu/system/files/publications/2373/TD0216072ENN.PDF
Accessed 8 July 2016

Hillebrand J, Olszewski D, Sedefov R. 2010. Legal highs on the Internet. *Subst Use Misuse*. 45(3):330-40. doi: 10.3109/10826080903443628. PubMed PMID: 20141450.
http://www.ncbi.nlm.nih.gov/pubmed/20141450

Ma A, English M. 2007. From Cradle to Grave -Tracking the life cycle of a drug is a complex process that early planning and IVR technology can help ease. *Applied Clinical Trials*. 16(7). Available at: http://www.appliedclinicaltrialsonline.com/cradle-grave Accessed 8 July 2016.

Ramsey J, Dargan PI, Smyllie M, Davies S, Button J, Holt DW, Wood DM. 2010. Buying 'legal' recreational drugs does not mean that you are not breaking the law. *QJM*. 103(10):777-83. doi: 10.1093/qjmed/hcq132. PubMed PMID: 20675395. http://www.ncbi.nlm.nih.gov/pubmed/20675395

Rose M, Leonard JM, Norman JC, Flanagan AY. 2015. *Novel Psychoactive Substances: Spice, Bath Salts, and Beyond*. NetCE • Sacramento, California. Available at: http://www.netcestudents.com/1272/Course_96910.pdf Accessed 8 July 2016.

UNODC. 2016. *World Drug Report 2016*. New York: United Nations. Available at: https://www.unodc.org/doc/wdr2016/WORLD_DRUG_REPORT_2016_web.pdf Accessed 8 July 2016

Table 1. Aspects/dimensions that could be considered by a 'life-cycle'/'natural history' approach to the study of NPS and relevant resources

Aspect/dimension	*Resources needed for data collection and analysis*
Hidden developments	
Original idea/concept/source for molecule	DeepWeb discussions amongst 'research chemists': The idea may be completely original as in creating a 'brand new' unique molecule or 'rediscovering' molecules in old patents (e.g. AH7941, MT-45), etc.
Creation of a name for molecule/product	DeepWeb activity monitoring
Offering for sale/advertising	DeepWeb activity monitoring; 'test purchases'; Law enforcement interdiction;
Mention in user discussion groups/fora	DeepWeb activity monitoring
Emergence into common view	
Appearance on surface net/in head shops etc.	Internet/media monitoring
Offers for sale/advertising	Internet/media monitoring; test purchasing; law enforcement interdiction;
Mention in user discussion groups/fora	Internet/media monitoring
Reports to treatment services	Mental health and drug service clients reports use of NPS
Health concerns	
Intoxications	Media reports; ambulance/ paramedic call-outs; presentations to Emergency Departments;
Severe adverse health consequences	Admissions to general hospital wards; psychiatric in-patient treatment; mental health and drug treatment service clients request help for problems caused by NPS; Calls to National Poison Information Services/ Toxbase inquiries;
Health Professional concerns	'Health alerts' issued; case reports in medical literature/ blogs; case series in medical literature;
Fatalities	Inquests/ Fatal Accident Inquiries (about 6 months after he event in the UK) or other judicial investigations; inclusion in official mortality statistics;
Forensic detections	
Unknown NPS in toxicology screenings	Amnesty bins; law enforcement drug confiscations; 'test purchases'; biological samples – drug driving, work-place testing, hospital admissions, post-mortem investigations;
Forensic professional concerns	Reports in chemical, toxicological, forensic, pathological blogs/ literature;
Social concerns	
Reports of 'incidents'	Media reports, reports to police, local authorities (e.g. trading standards); concerns expressed by 'interest' groups; etc.
Coverage in surveys	Inclusion of suitable questions in surveys of different population groups, both paper-based and electronic, whether online or face to face any of the following scenarios – music concerts/ festivals, etc.; presentations to health professionals; arrest and imprisonment; etc.
Official responses	
Risk assessments	Local (administrative areas), national (country), international – European Union, WHO.
Temporary regulation/control	Local (administrative areas), national (country), international – European Union, INCB
Permanent regulation/control	Local (administrative areas), national (country), international – European Union, WHO & UNODC
Advice on treatment	Guidance issued by health professionals' bodies; WHO
Advice on forensic/chemical analyses	Guidance from international professional associations; UNODC
Advice on medical classification	Guidance from Euro-Stat/WHO on ICD coding (advice needed for ICD10 and 11)
Effects of regulation/control	Availability, price, purity, hospital admissions, deaths, demand for treatment, etc.
Long-term monitoring	Prevalence, emergence of health harms from long-term use; Advice on monitoring from EMCDDA and UNODC
Acronyms: EMCDDA – European Monitoring Centre for Drugs and Drug Addiction; ICD – International Classification of Diseases; INC – International Narcotics Control Board; UNODC – United Nations Office for Drugs and Crime; WHO – World Health Organization; UNODC	

From concept(ion) to life after death/the grave: the 'natural' history and life-cycle(s) of Novel Psychoactive Substances (NPS)

WHY DO WE NEED TO KNOW NOW ABOUT THE LONGEVITY/EXISTENCE OF NOVEL PSYCHOACTIVE SUBSTANCES (NPS)?

New or novel psychoactive substances are not a recent phenomenon. In the latter decades of the twentieth century new psychoactive substances such as ecstasy (MDMA), 'crack' cocaine and methylamphetamine emerged onto the international recreational drug scene. The phenethylamine 2C-T-7, first synthesised in 1986, was described in detail in the Shulgins' PIKHAL book (Shulgin & Shulgin, 1991) leading to dissemination of data relating to it. By 1997 it was possible to purchase this compound from Dutch and German 'smart' shops. Street-level availability was very low by the early 2000s, but a survey of internet websites indicated a somewhat different scenario both in terms of information about it and opportunities for purchase Schifano *et al*., 2005). Since 2005 there have been only occasional confiscations and case-reports or academic papers concerning 2C-T-7.

However, during the first decade of the present century, the 'noughties', there was a marked step-change in this phenomenon – an increasingly accelerated rate of appearance of new or novel substances contrasted with the substances above which are now part of the 'traditional' or established drug scene. Since 2005 this development has been accompanied by increases in the number and variety of molecules and products offered to (potential) consumers (EMCDDA-EUROPOL, 2016; UNODC, 2016). At present, there appears to be little prospect of the situation changing in the short-term.

The accelerating speed and extent of these changes is causing a number of important challenges to various constituencies or stake-holders including: policy-makers, law enforcement agencies, treatment services, epidemiologists, communities and, not least of all, consumers. The key challenges are: how are NPS being created or 'discovered'; what is appearing and when; are they related to existing known molecules; who is producing them and where; how are NPS being advertised and distributed; what is their legal status; what social consequences might arise; what are their likely properties; which and how many adverse health effects, morbidity or mortality can they cause; what the appropriate treatments are; what services might be impacted and how, and over what time-scale(s).

Briefly, these challenges arise from the fact that most NPS are unknown quantities in that they have not been subject to any type(s) of prior testing; therefore, their psychoactive properties (if any), pharmacological, neurophysiological, neuropsychological, psychopharmacological, toxicological, and addiction potential attributes remain unclear. Furthermore, the contents of NPS/'legal high' products offered for sale are unknown to law enforcement agencies, retailers, potential purchasers/consumers, health professionals, etc. and may change over time (Davies *et al*., 2010; Ramsey *et al*., 2010).

The challenges thrown up by this lack of information make it difficult to know if it is necessary to respond to the emergence of a particular molecule and, if a response is considered appropriate, what form(s) that might take. Part of any strategy that needs to be in place for such considerations ought to include an assessment of how long that molecule may remain in circulation and what may be the possible consequences.

One way of assessing how long a molecule may be around would be to compare its known characteristics with that of similar molecules and what happened to them. This means charting the existence of a number of psychoactive substances, including new or novel ones, in order to establish base-lines against which predictive models could be developed and tested. In other words, a series of life-cycles or natural histories of how 'traditional' recreational drugs and NPS evolve need to be documented.

CONCEPTUAL APPROACH

A common approach in describing the stages in the production and consumption of goods is to look at their journey using such metaphors as "from field to fork" or "life is a journey" from "birth to death" or "cradle to grave". In the psychoactive substances field, we developed a conceptual framework for classifying mortality associated with each stage of the khat plant's journey from its cultivation, transportation, consumption, to its effects on the human body. Specifically, we utilised evidence abstracted from observed phenomena derived from a range of sources along that journey to provide a vehicle to identify factors that may impact on the phenomenon of khat-related mortality (Corkery *et al*., 2011).

It is now proposed that a similar approach could be applied to the phenomenon of psychoactive substances, both 'traditional' and 'novel'/'new'. The aim would be to identify initially what the overall timeline and scale is for psychoactive substances, especially 'legal highs'/novel psychoactive substances (NPS), from original concept or creation through to death (of human individuals), or even beyond, i.e. their survival, demise or change following regulation/control.

So far as can be ascertained from internet searches using Google and Google Scholar, this is the first time this approach has been mooted in the published literature in the field of substance (ab)use. However, the notion of "cradle to grave" tracking or monitoring over the life cycle of investigational/experimental products is used in the field of pharmaceutics for accountability, reconciliation, destruction, etc. throughout a product's life cycle (Ma *et al*., 2007; Edwards, 2008). The word 'generation' has been used in recent years to describe new psychoactive products and molecules created and released to replace those existing ones coming under control as a result of legislative actions.

The term 'drug epidemic cycle' (Rose *et al*., 2015) has been used to describe the process by which a 'recreational' drug is first used within a narrowly-defined population or community before becoming main-stream (e.g. the use of methamphetamine in the 'gay' community before moving into the 'club scene') possibly because of its perceived safety, desired effects, and legality before leading to adverse health consequences, then controls, and perhaps leading to reduced consumption. However, this notion does not capture the possibility of re-emergence. Furthermore, 'epidemic' is an inaccurate term in this context.

ASPECTS TO COVER

In the context of the EPS/NPS project (http://www.npsproject.eu/), the authors are involved in studying the role(s) of the Internet, especially the DeepWeb, in the creation, availability, sale, distribution of substances, and dissemination of information about NPS. The idea emerged during a 'brain-storming' session that the earliest indication of the possible appearance of a new substance might be evidenced on the DeepWeb, thereby giving a 'heads-up' or advance warning to relevant stake-holders. This thought was subsequently elaborated into the notion

that there may be benefits in looking at the life-cycle or natural history and evolution of specific NPS. Key aspects to try and document include: first appearance on the DeepWeb; migration to the Surface Net or open Internet; move into 'head-shops' and/or the 'street' market; notification to formal Early Warning Systems; implementation of legislation to counter the substance; effects of legislation/regulation on availability/use or displacement/substitution; and whether NPS suffer a demise, rebirth/reincarnation/resurrection or alteration/mutation/reinvention. Further details of these aspects and relevant resources are given in Table 1; this is not an exhaustive list.

HOW COULD THIS RESEARCH BE DONE?

Both retrospective and prospective collection of data on NPS and other substances, including those already regulated or controlled would be required in order to get a complete profile of 'traditional' and newly emerging/re-emerging psychoactive substances. Prospective data collection would have to be undertaken on a regular and systematic basis, perhaps with a periodicity as short as a week.

We conjecture that data pointing to the existence of new NPS would first emerge on the DeepWeb - especially DeepNets - before appearing on the Surface Net (Internet) and will be less visible, in line with the clandestine nature of drug use and supply. Therefore, it might be sensible to monitor discussion groups/fora (across several domains/areas of interest – not just users) at specified intervals, say every 2 or 3 weeks, and to take copies/snap-shots of the sites/web-pages to see how things develop over time, and also to see how long it takes before substances are found on the Surface Net.

Methods for online monitoring of the Internet developed by previous projects such as Psychonaut (Deluca *et al*., 2012), ReDNet (Corazza *et al*., (2013), and EU-MADNESS (http://www.eumadness.eu/) would need to be adapted and refined for DeepWeb monitoring as part of the Enhancing Police EPS/NPS project (http://www.npsproject.eu/) and any future work. The key difference would be the use of an Internet communication method intended to enable online anonymity such as TOR (https://www.torproject.org/) when monitoring the DeepWeb, and suitable search engines, e.g. grams (https://www.deepdotweb.com/2014/04/08/grams-darknetmarkets-search-engine/). Search strategies and search terms would need to be developed to monitor the different types of websites, open and hidden, as outlined in Table 1.

Access to other data, including databases, professional networks, and access to informed stake-holders such as members of early warning systems would need to be developed and maintained so that detailed information relating to the data given in Table 1 can be collected on a systematic and routine basis. The types of data to be collected would need to be agreed by participating researchers and data-providers, along with data-sharing and confidentiality protocols, etc. Compilation of data from this multi-disciplinary approach should be centrally co-ordinated, and held in secure conditions with appropriate levels of access.

The aim of the data collection would be to collect data that will lend themselves to the development of mathematical models that will validate existing and new knowledge of 'traditional' recreational substances and facilitate predictions regarding the likely stages and time-scales in the life-cycles of NPS.

LIKELY OUTCOMES OF SUCH RESEARCH

There may be different time-scales for different types of 'traditional' and legal drugs as well as NPS. Old medicines discontinued because of adverse side-effects 'rediscovered' from scanning the patent databases may have a far longer life-story than newer/current medications being abused (e.g. modafinil) or new molecules created to avoid new regulations/controls (e.g. methylphenidate derivatives), but having a shorter history than natural products/plants used for centuries in folk-medicine/religious activities, etc.

This approach should make it faster to track the 'historical evolution of an emerging NPS'. It could be possible to collect more information on a specified drug without waiting for its appearance. The potential insights that could be generated by the proposed approach cover five main domains. First, change over time in: developments in the uses, modes of administration, formulations/preparations, content of products, marketing, supply chains, prices, purities, quantities offered. Second, their first appearance on discussion fora/posts. Third, their first appearance on drug market sites. Fourth, how their markets/availability/attractiveness changes over time, and how these aspects change depending on legal status/notification in a specified country, etc. The legal status of specific molecules may differ in various countries, thereby leading to different patterns in terms of drug availability, use, treatment, etc. Lastly, health risks (acute and chronic physical/mental), morbidity, mortality associated with NPS (production and/or consumption).

However, some considerations will need to be borne in mind. Many NPS appearing as 'products' may be marketed with the same packaging but contain different compounds (Davies *et al*., 2010; Ramsey *et al*., 2010). In addition, the same 'branded' compound may contain different NPS or concentrations in different countries and/or at different times (Corazza *et al*., 2014). Therefore, if data are only collected from websites without testing/verifying the chemical composition of these drugs, researchers could collect 'clinical' and 'marketing' data not necessarily associated with an identified chemical composition (Hillebrand *et al*., 2010).

CONCLUSIONS

Taking a holistic approach to NPS allows researchers to identify/think of wider range of dimensions of a phenomenon and what factors may impact on it and how these might be influenced/ tackled in the future if desired/thought practical in order to affect changes. There will be implications for service provision, treatment options, interdiction, monitoring/ surveillance, pharmacovigilance, epidemiology, law-making, education, etc. The approach advocated here should mean that it could be easier to identify which NPS are likely to come up or are emerging in real time, and, therefore, pre-empt/prevent their supply. The lag which academic research currently experiences in respect of the online NPS market (Deluca *et al*., 2012) should be reduced.

FUNDING

This paper was supported in part by grants of the European Commission Project EPS/NPS-Enhancing Police Skills concerning Novel Psychoactive Substances, with the financial support of the European Commission – Targeted call on cross border law enforcement cooperation in the field of drug trafficking - DG Justice/DG Migrations and Home Affairs (JUST/2013/ISEC/DRUGS/AG/6429). http://www.npsproject.eu/

CONFLICTS OF INTEREST

The authors declare that there is no conflict of interest.

REFERENCES

Corazza O, Assi S, Simonato P, Corkery J, Bersani FS, Demetrovics Z, Stair J, Fergus S, Pezzolesi C, Pasinetti M, Deluca P, Drummond C, Davey Z, Blaszko U, Moskalewicz J, Mervo B, Furia LD, Farre M, Flesland L, Pisarska A, Shapiro H, Siemann H, Skutle A, Sferrazza E, Torrens M, Sambola F, van der Kreeft P, Scherbaum N, Schifano F. Promoting innovation and excellence to face the rapid diffusion of novel psychoactive substances in the EU: the outcomes of the ReDNet project. 2013. *Hum Psychopharmacol*. 28(4):317-23. doi: 10.1002/hup.2299. PubMed PMID: 23881879.
http://www.ncbi.nlm.nih.gov/pubmed/23881879

Corazza O, Valeriani G, Bersani FS, Corkery J, Martinotti G, Bersani G, Schifano F. "Spice," "kryptonite," "black mamba": an overview of brand names and marketing strategies of novel psychoactive substances on the web. 2014. *J Psychoactive Drugs*. 46(4):287-94. doi: 10.1080/02791072.2014.944291. PubMed PMID: 25188698.
https://www.ncbi.nlm.nih.gov/pubmed/25188698

Corkery JM, Schifano F, Oyefeso A, Ghodse AH, Tonia T, Naidoo V, Button J. 2011. Overview of literature and information on "khat-related" mortality: a call for recognition of the issue and further research. *Ann Ist Super Sanita*. 47(4):445-64. doi: 10.4415/ANN_11_04_17. PubMed PMID: 22194080.
http://www.ncbi.nlm.nih.gov/pubmed/22194080

Davies S, Wood DM, Smith G, Button J, Ramsey J, Archer R, Holt DW, Dargan PI. 2010. Purchasing 'legal highs' on the Internet--is there consistency in what you get? *QJM*. 103(7):489-93. doi: 10.1093/qjmed/hcq056. PubMed PMID: 20413562.
http://www.ncbi.nlm.nih.gov/pubmed/20413562

Deluca P, Davey Z, Corazza O, Di Furia L, Farre M, Flesland LH, Mannonen M, Majava A, Peltoniemi T, Pasinetti M, Pezzolesi C, Scherbaum N, Siemann H, Skutle A, Torrens M, van der Kreeft P, Iversen E, Schifano F. 2012. Identifying emerging trends in recreational drug use; outcomes from the Psychonaut Web Mapping Project. *Prog Neuropsychopharmacol Biol Psychiatry*. 39(2):221-6. doi: 10.1016/j.pnpbp.2012.07.011. PubMed PMID: 22841965.
http://www.ncbi.nlm.nih.gov/pubmed/22841965

Edwards AG. 2008. Quality Systems for Drugs and Biologics - FDA is modernizing and streamlining current good manufacturing practices. *Pharmaceutical Technology*. 32(2). Available at: http://www.pharmtech.com/quality-systems-drugs-and-biologics-0?id=&sk=&date=&&pageID=1
Accessed 8 July 2016.

European Monitoring Centre for Drugs and Drug Addiction and Europol. 2016. EU Drug Markets Report: In-Depth Analysis, EMCDDA–Europol Joint publications, Publications Office of the European Union, Available at:
http://www.emcdda.europa.eu/system/files/publications/2373/TD0216072ENN.PDF

Accessed 8 July 2016

Hillebrand J, Olszewski D, Sedefov R. 2010. Legal highs on the Internet. *Subst Use Misuse*. 45(3):330-40. doi: 10.3109/10826080903443628. PubMed PMID: 20141450. http://www.ncbi.nlm.nih.gov/pubmed/20141450

Ma A, English M. 2007. From Cradle to Grave -Tracking the life cycle of a drug is a complex process that early planning and IVR technology can help ease. *Applied Clinical Trials*. 16(7). Available at: http://www.appliedclinicaltrialsonline.com/cradle-grave Accessed 8 July 2016.

Ramsey J, Dargan PI, Smyllie M, Davies S, Button J, Holt DW, Wood DM. 2010. Buying 'legal' recreational drugs does not mean that you are not breaking the law. *QJM*. 103(10):777-83. doi: 10.1093/qjmed/hcq132. PubMed PMID: 20675395. http://www.ncbi.nlm.nih.gov/pubmed/20675395

Rose M, Leonard JM, Norman JC, Flanagan AY. 2015. *Novel Psychoactive Substances: Spice, Bath Salts, and Beyond*. NetCE • Sacramento, California. Available at: http://www.netcestudents.com/1272/Course_96910.pdf Accessed 8 July 2016.

Schifano F, Deluca P, Agosti L, Martinotti G, Corkery JM, Alex B, Caterina B, Heikki B, Raffaella B, Anna C, Lucia DF, Dorte DR, Magi F, Susana F, Irene F, Claude G, Lisbet H, Lene SJ, Mauro L, Christopher L, Aino M, Teuvo P, Milena P, Salman R, Damien R, Angela RM, Francesco R, Norbert S, Holger S, Josep T, Marta T, Francesco Z; Psychonaut 2002 Research Group. New trends in the cyber and street market of recreational drugs? The case of 2C-T-7 ('Blue Mystic'). 2005. *J Psychopharmacol*. 19(6):675-9. PubMed PMID: 16272191. doi: 10.1177/0269881105056660 http://www.ncbi.nlm.nih.gov/pubmed/16272191

Shulgin A., & Shulgin A. 1991. *PIHKAL: a chemical love story*. California: Transform Press. Available at: https://erowid.org/library/books_online/pihkal/pihkal.shtml Accessed 2 October 2016.

UNODC. 2016. *World Drug Report 2016*. New York: United Nations. Available at: https://www.unodc.org/doc/wdr2016/WORLD_DRUG_REPORT_2016_web.pdf Accessed 8 July 2016

Table 1. Aspects/dimensions that could be considered by a 'life-cycle'/'natural history' approach to the study of NPS and relevant resources

Aspect/dimension	*Resources needed for data collection and analysis*
Hidden developments	
Original idea/concept/source for molecule	DeepWeb discussions amongst 'research chemists': The idea may be completely original as in creating a 'brand new' unique molecule or 'rediscovering' molecules in old patents (e.g. AH7941, MT-45), etc.
Creation of a name for molecule/product	DeepWeb activity monitoring
Offering for sale/advertising	DeepWeb activity monitoring; 'test purchases'; Law enforcement interdiction;
Mention in user discussion groups/fora	DeepWeb activity monitoring
Emergence into common view	
Appearance on surface net/in head shops etc.	Internet/media monitoring
Offers for sale/advertising	Internet/media monitoring; test purchasing; law enforcement interdiction;
Mention in user discussion groups/fora	Internet/media monitoring
Reports to treatment services	Mental health and drug service clients reports use of NPS
Health concerns	
Intoxications	Media reports; ambulance/ paramedic call-outs; presentations to Emergency Departments;
Severe adverse health consequences	Admissions to general hospital wards; psychiatric in-patient treatment; mental health and drug treatment service clients request help for problems caused by NPS; Calls to National Poison Information Services/ Toxbase inquiries;
Health Professional concerns	'Health alerts' issued; case reports in medical literature/ blogs; case series in medical literature;
Fatalities	Inquests/ Fatal Accident Inquiries (about 6 months after he event in the UK) or other judicial investigations; inclusion in official mortality statistics;
Forensic detections	
Unknown NPS in toxicology screenings	Amnesty bins; law enforcement drug confiscations; 'test purchases'; biological samples – drug driving, work-place testing, hospital admissions, post-mortem investigations;
Forensic professional concerns	Reports in chemical, toxicological, forensic, pathological blogs/ literature;
Social concerns	
Reports of 'incidents'	Media reports, reports to police, local authorities (e.g. trading standards); concerns expressed by 'interest' groups; etc.
Coverage in surveys	Inclusion of suitable questions in surveys of different population groups, both paper-based and electronic, whether online or face to face any of the following scenarios – music concerts/ festivals, etc.; presentations to health professionals; arrest and imprisonment; etc.
Official responses	
Risk assessments	Local (administrative areas), national (country), international – European Union, WHO.
Temporary regulation/control	Local (administrative areas), national (country), international – European Union, INCB
Permanent regulation/control	Local (administrative areas), national (country), international – European Union, WHO & UNODC
Advice on treatment	Guidance issued by health professionals' bodies; WHO
Advice on forensic/chemical analyses	Guidance from international professional associations; UNODC
Advice on medical classification	Guidance from Euro-Stat/WHO on ICD coding (advice needed for ICD10 and 11)
Effects of regulation/control	Availability, price, purity, hospital admissions, deaths, demand for treatment, etc.
Long-term monitoring	Prevalence, emergence of health harms from long-term use; Advice on monitoring from EMCDDA and UNODC

Acronyms: EMCDDA – European Monitoring Centre for Drugs and Drug Addiction; ICD – International Classification of Diseases; INC – International Narcotics Control Board; UNODC – United Nations Office for Drugs and Crime; WHO – World Health Organization; UNODC